REVIEW ARTICLE

Heart, Lung and Vessels. 2013; 5(4): 227-245

Levosimendan: current data, clinical use and future development

M.S. Nieminen[1], S. Fruhwald[2], L.M.A. Heunks[3], P.K. Suominen[4], A.C. Gordon[5], M. Kivikko[6], P. Pollesello[6]

[1]Heart and Lung Center, University of Helsinki Central Hospital, Helsinki, Finland; [2]Medizinische Universität, Graz, Austria; [3]Radboud University Medical Center Nijmegen, Nijmegen, The Netherlands; [4]Department of Anesthesia and Intensive Care, Children's Hospital, Helsinki, Finland; [5]Imperial College/Charing Cross Hospital, London, UK; [6]Orion Pharma, Espoo, Finland

Heart, Lung and Vessels. 2013; 5(4): 227-245

ABSTRACT

Levosimendan is an inodilator indicated for the short-term treatment of acutely decompensated severe chronic heart failure, and in situations where conventional therapy is not considered adequate. The principal pharmacological effects of levosimendan are (a) increased cardiac contractility by calcium sensitisation of troponin C, (b) vasodilation, and (c) cardioprotection. These last two effects are related to the opening of sarcolemmal and mitochondrial potassium-ATP channels, respectively. Data from clinical trials indicate that levosimendan improves haemodynamics with no attendant significant increase in cardiac oxygen consumption and relieves symptoms of acute heart failure; these effects are not impaired or attenuated by the concomitant use of beta-blockers. Levosimendan also has favourable effects on neurohormone levels in heart failure patients. Levosimendan is generally well tolerated in acute heart failure patients: the most common adverse events encountered in this setting are hypotension, headache, atrial fibrillation, hypokalaemia and tachycardia. Levosimendan has also been studied in other therapeutic applications, particularly cardiac surgery - in which it has shown a range of beneficial haemodynamic and cardioprotective effects, and a favourable influence on clinical outcomes - and has been evaluated in repetitive dosing protocols in patients with advanced chronic heart failure. Levosimendan has shown preliminary positive effects in a range of conditions requiring inotropic support, including right ventricular failure, cardiogenic shock, septic shock, and Takotsubo cardiomyopathy.

Keywords: *levosimendan, acute heart failure, cardiac surgery, cardioprotective inodilator, review, shock.*

INTRODUCTION

Interest in developing new drugs for the treatment of acute heart failure (AHF) remains high and the past, present and future of diuretics, vasodilators and inotropes is source of debate and expectations (1).

Among these three drug therapies, is the inotropic one which is raising the most controversies (2). While waiting for new promising drugs to be confirmed as serious players (3), the present manuscript aims to review the latest addition to the available repertoire of inotropes and inodilators, levosimendan (*Figure 1)*.

Levosimendan is an inodilator developed for intravenous use in hospitalised patients with acutely decompensated heart failure (ADHF). The pharmacological effects of levosimendan are:

a) increased cardiac contractility mediated by calcium sensitisation of troponin C (4-8);
b) vasodilation through the opening of potassium channels on the sarcolemma of smooth muscle cells in the vasculature (9-12);

Corresponding author:
Piero Pollesello, PhD., Adj. Prof.
Critical Care Proprietary Products Division
Orion Pharma, Orion Corporation
P.O. Box 65, FIN-02101 Espoo, Finland
e-mail: piero.pollesello@orionpharma.com

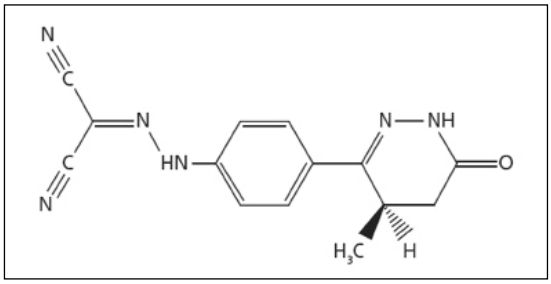

Figure 1 - *Chemical structure of levosimendan, the (-) enantiomer of {[4-(1,4,5,6-tetrahydro-4-methyl-6-oxo-3-pyridazinyl)phenyl]hydrazono}propanedinitrile.*

c) cardioprotection through the opening of mitochondrial potassium channels in the cardiomyocytes (13-16).

Clinical data from heart failure patients show that levosimendan improves haemodynamics (17-19) without a significant increase in oxygen consumption (20, 21), reduces symptoms of AHF (17, 18, 22, 23), has a beneficial effect on neurohormone levels (22-24), has a sustained efficacy due to formation of an active metabolite (24, 25), and suffers no loss of effect in patients under beta-blockade (17, 26). Levosimendan offers a predictable safety profile (17-19, 23), no impairment of diastolic function (27, 28), with no development of tolerance (25). The most common adverse events are hypotension, headache, atrial fibrillation, hypokalemia and tachycardia (22, 23, 29).

Levosimendan is indicated for the short-term treatment of acutely decompensated severe chronic heart failure in situations where conventional therapy is not sufficient, and in cases where inotropic support is considered appropriate. In the latest decade, however, levosimendan has been studied in numerous clinical trials outside the field of acute heart failure. Primarily, the drug has been tested in the cardiac surgery settings (30), field in which the drug has shown beneficial haemodynamic and cardioprotective effects and a favorable outcome effect. In addition, several studies with repetitive levosimendan dosing in patients suffering from advanced chronic heart failure have shown beneficial effects on haemodynamics, neurohormone levels and symptoms (31). Finally, levosimendan has also shown preliminary positive effects - mainly in small-scale studies - in right ventricular failure, cardiogenic shock, septic shock, Takotsubo cardiomyopathy, and in other states requiring inotropic support (32, 33). Our aim is to review the current data, clinical use and future development of levosimendan in all therapy settings envisioning the future development for this drug, the first in class of the cardioprotective inodilators.

Table 1 - *Trial acronyms.*

ALARM-HF	Acute Heart Failure Global Survey of Standard Treatment
LIDO	Levosimendan Infusion versus Dobutamine
LevoRep	Randomised trial investigating the efficacy and safety of pulsed infusions of levosimendan in outpatients with advanced heart failure
REVIVE I and II	Randomized Multicenter Evaluation of Intravenous Levosimendan Efficacy trials I and II
RUSSLAN	Randomized Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure after an Acute Myocardial Infarct
SURVIVE	Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support

CLINICAL DEVELOPMENT

Most of the studies in the regulatory clinical development of levosimendan were (*Table 1*) performed in patients with acute worsening of chronic heart failure. The

regulatory clinical development program included about 3,500 patients.

Dose-finding study

The therapeutic dose range of levosimendan administered over a 24 h period was identified in a double-blind, placebo-controlled study including 151 patients with stable (mainly NYHA class III) heart failure of ischaemic origin. Patients were treated with a bolus dose of levosimendan of 3-36 μg/kg in 10 min followed by a 24 h intravenous infusion at doses ranging from 0.05 to 0.6 μg/kg/min (19).

Dose escalation study

Up-titration, maintenance and withdrawal of levosimendan were studied in a randomised, double-blind, placebo-controlled study in 146 patients hospitalised for decompensated heart failure (NYHA class III or IV) due to coronary artery disease (60 %) or dilated cardiomyopathy (40 %) (18). Patients received an intravenous infusion of levosimendan at doses ranging from 0.1 to 0.4 μg/kg/min.

The study was divided into three phases. During the first 6 h, escalated doses of levosimendan (n = 98) were compared with placebo (n = 48). From 6 to 24 h, patients in the levosimendan group continued to receive the study medication as an open-label infusion. At 24 h, the patients remaining in the study were randomised to continue on levosimendan (levosimendan continuation group) or placebo (levosimendan withdrawal group), administered double-blind up to 48 h (18, 25).

LIDO study

Levosimendan was compared with dobutamine in the LIDO (Levosimendan Infusion versus Dobutamine) study, a double-blind, randomised study in 203 patients with low-output heart failure, who required right heart catheterisation and treatment with an intravenous inotropic drug. Patients randomised to levosimendan were treated with an initial intravenous bolus of 24 μg/kg in 10 min, followed by a 24 h intravenous infusion of levosimendan at doses from 0.1 to 0.2 μg/kg/min (17).

RUSSLAN study

The safety of levosimendan in patients with left ventricular failure complicating an acute myocardial infarction was studied in RUSSLAN (Randomised Study on Safety and Effectiveness of Levosimendan in Patients with Left Ventricular Failure after an Acute Myocardial Infarct), a placebo-controlled, double-blind, parallel-group, randomised study in 504 patients enrolled within 5 days of an index infarction (34). Patients randomised to levosimendan were treated with a bolus dose of 6-24 μg/kg in 10 min, followed by a 6-h intravenous infusion at rates ranging from 0.1 to 0.4 μg/kg/min. Invasive haemodynamic data were not collected.

REVIVE studies

The REVIVE (Randomised Multicenter Evaluation of Intravenous Levosimendan Efficacy) studies (REVIVE I and REVIVE II) evaluated the efficacy of levosimendan on symptoms of heart failure by means of a composite endpoint comprising patients' subjective symptom assessments (at 6 h, 24 h and 5 days) and signs of worsening symptoms (including death) during the 5 days after starting a 24 h trial drug infusion. These two randomised, double-blind, placebo-controlled, parallel-group studies in patients with ADHF were conducted mainly in the USA. REVIVE I (n = 100) was a pilot study designed to evaluate the suitability of the chosen composite (35); REVIVE II (n = 600) was a phase III study (22). Patients randomised to levosimendan (given in addition to current medications) received an initial bolus of 6-12 μg/kg in 10

min, followed by a 24 h intravenous infusion at rates of 0.1 to 0.2 µg/kg/min.

SURVIVE study

The SURVIVE (Survival of Patients with Acute Heart Failure in Need of Intravenous Inotropic Support) study was a double-blind, randomised study in 1327 patients with severe systolic heart failure comparing the effects of levosimendan with dobutamine on mortality. Patients in the levosimendan arm were treated (on top of current AHF medications) with a bolus of 12 µg/kg in 10 min, followed by a 24 h intravenous infusion of 0.1 to 0.2 µg/kg/min (23).

MAIN THERAPEUTIC EFFICACY AND SAFETY DATA

Haemodynamics

Levosimendan has repeatedly been shown to produce significant dose-dependent increases in cardiac output, stroke volume and heart rate, and decreases in pulmonary capillary wedge pressure, mean blood pressure, mean pulmonary artery pressure, mean right atrial pressure and total peripheral resistance (19).

The effect of levosimendan on haemodynamic variables (cardiac output, stroke volume, heart rate and pulmonary capillary wedge pressure) are clearly evident already at the end of a 5 min bolus infusion (36). There is no sign of development of tolerance even with a prolonged infusion up to 48 h (25). Haemodynamic effects are maintained up to 7-9 days after stopping levosimendan infusion, due to the formation of an active metabolite, designated OR-1896 (24).

Compared with dobutamine, levosimendan produces a slightly greater increase in cardiac output and a profoundly greater decrease in pulmonary capillary wedge pressure (17, 37). In contrast to dobutamine, the haemodynamic effects are not attenuated with concomitant beta-blocker use (17). At 48 h after the start of infusion in beta-blocked patients with severe ADHF, a 24 h infusion of levosimendan achieves better haemodynamic effects than a 48 h dobutamine infusion (37).

Blood pressure

The data from REVIVE show that levosimendan significantly decreases blood pressure compared to placebo (22). Accordingly, the current Summary of Product Characteristics (SPC) labelling suggests levosimendan be used with caution in patients with low baseline systolic or diastolic blood pressure or those at risk for a hypotensive episode.

Post-hoc analyses of the REVIVE studies identified systolic blood pressure < 100 mmHg or diastolic blood pressure < 60 mmHg at baseline as a factor increasing mortality risk (22, 38). Conversely, in patients with higher blood pressure at baseline (systolic ≥100 mmHg and diastolic ≥60 mmHg), mortality was 8 % with levosimendan and 9 % with placebo ($p = 0.81$). Of importance is the finding that the primary composite endpoint was still positive and statistically significant in this subgroup (38).

Symptoms

Dyspnoea improved in significantly more patients treated with levosimendan compared with placebo at 6 hours after the start of treatmentin one early controlled trial in severe heart failure (18). On the other hand, in the LIDO study (17), symptoms of dyspnoea and fatigue improved equally well in levosimendan-or dobutamine-treated patients at 24 h after the start of infusion.

In the REVIVE II study, symptoms over the 5-day assessment period improved significantly more with levosimendan than

with placebo (22). It should be noted that in REVIVE levosimendan (or placebo) was administered on top of the standard of care and that in the placebo group, the majority of the patients also improved vs baseline.

Composite end point

In the REVIVE II study, the primary endpoint was a composite consisting of patients' subjective symptom assessments (at 6 hours, 24 hours, and 5 days) and signs of worsening symptoms (including death) during the 5 days after starting a 24-h trial drug infusion. Improvement was observed more frequently (19 % vs 15 %) and worsening less frequently (19 % vs 27 %) in levosimendan treated patients compared with placebo ($p = 0.015$) (22). The improvement in the composite endpoint was accompanied by a lower need for rescue medication in the levosimendan group (22, 38).

Neurohormones

Several studies indicate that levosimendan produces a rapid and sustained decrease in natriuretic peptides. Lilleberg et al. (24) found that a 24-h levosimendan infusion induced a 40 % decrease in plasma N-terminal atrial natriuretic peptide and N-terminal pro-BNP (NT-proBNP) levels and the treatment effect was estimated to last up to 16 and 12 days, respectively. In the SURVIVE study, a similar decrease in BNP was seen (23) but duration of the effect could not be determined as the last time-point for measuring BNP was 5 days. In the REVIVE II study the significant effect on BNP was also evident until day 5 (22).

Mortality

In the LIDO study, mortality was followed as a secondary endpoint for 31 days. During that time, 8 % of patients assigned to levosimendan died, compared with 17 % assigned to dobutamine ($p = 0.049$). The follow-up was retrospectively extended to 180 days, at which point the respective figures were 26 % for levosimendan and 38 % for dobutamine ($p = 0.029$) (17). Mortality in the RUSSLAN study (34) was prospectively followed for 14 days after starting treatment and shown to be significantly lower with levosimendan than with placebo (12 % vs 20 %; $p = 0.031$). There was a trend for this positive effect to persist up to 180 days in a retrospective analysis (23 % vs 31 %; $p = 0.053$). In the REVIVE II study (22), mortality was numerically, but not statistically significantly, higher in the levosimendan group, with 45 (15 %) deaths in the levosimendan group and 35 (12 %) in the placebo group during the 90-day study period ($p = 0.21$). In the SURVIVE study (23) there was no significant difference in survival between levosimendan and dobutamine (26 % vs 28 %, hazard ratio 0.91; 95 % CI, 0.74-1.13; $p = 0.40$). A majority (88 %) of patients in this study had a history of ADHF. In these patients, mortality at 31 days was significantly lower with levosimendan than with dobutamine ($p = 0.046$) (26). Similarly, mortality was significantly lower with levosimendan than with dobutamine in the subset of patients receiving concomitant beta-blockers (26).

Several meta-analyses on the effect of levosimendan on mortality have been recently published (39-44). Among these, the investigation by Landoni et al. (40) is the most comprehensive and statistically the most robust. It included 45 clinical trials with intravenous levosimendan with a total of 5480 patients. Levosimendan significantly reduced mortality both in cardiology and cardiac surgery settings, and both against dobutamine and placebo.

A registry study, ALARM-HF (Acute Heart Failure Global Survey of Standard Treatment), reviewed in-hospital treatments in eight countries (45). Unadjusted analysis showed a significantly higher in-hospital mortality rate in patients receiving intra-

venous inotropes (25.9 %) compared to those who did not (5.2 %) ($p < 0.0001$). A propensity-based analysis was performed to compare in-hospital mortality in patients treated only with intravenous levosimendan versus those treated only with catecholamines within 24 h of therapy initiation. Propensity score matching produced 104 matched pairs and showed that the use of levosimendan resulted in a significant reduction in the risk of in-hospital mortality (hazard ratio 0.25, 95 % CI 0.07-0.85).

Hospitalization

A way to evaluate the effect of a medication on both mortality and morbidity is to assess the number of days a patient is both alive and out of hospital during the follow-up period. In the LIDO study, patients in the levosimendan group spent significantly more days alive and out of hospital than dobutamine-treated patients in a retrospective 180-day follow-up analysis (median 157 vs 133 days for levosimendan and dobutamine, respectively; $p = 0.027$) (17).

In the REVIVE II study, the mean duration of the initial hospitalisation was almost 2 days shorter in the levosimendan group (7.0 days) than in the placebo group (8.9 days) (22, 38). Significantly more patients treated with levosimendan were released within 5 days and fewer had extended hospitalisations ($p = 0.008$).

In a recent single center study (46) that compared levosimendan with standard of care in a population of AHF patients, the mean length of hospitalization was 12.1 and 13.6 days in the levosimendan ($n = 147$) and control groups ($n = 147$), respectively ($p < 0.05$). Re-hospitalization rates were lower in the levosimendan group at 12 months (7.6 vs 14.3 %; $p < 0.05$), and mortality rates at 1 month were 2.1 % vs 6.9 %, respectively ($p < 0.05$). In conformity with these observations from individual studies, in the earlier-mentioned meta-analysis by Landoni et al. (40) the mean length of stay in hospital was 1.59 (95 % CI 0.85-2.33) days shorter in levosimendan-treated patients in the cardiology setting ($p < 0.0001$).

Renal function

Renal function often worsens in patients with AHF, and this deterioration is associated with adverse outcome. Studies show improved serum creatinine levels in levosimendan-treated patients (47, 48).

Estimated glomerular filtration rate (eGFR) improved in levosimendan compared to dobutamine treated patients with heart failure who required inotropic therapy (49). A placebo-controlled study in patients hospitalized for decompensated heart failure and renal dysfunction, showed a statistically significant improvement in eGFR in levosimendan treated patients. Peak effect was seen at 3 days after a 24-h infusion, with discernible effects persisting up to 14 days (50). In addition to beneficial effects on central hemodynamics, levosimendan has direct effects on renal circulation and induces preglomerular vasodilation (51), leading to improved renal blood flow and glomerular filtration rate (52). The renal oxygen demand/supply relationship is not affected by levosimendan (51). In a meta-analysis of 4 randomized studies on the effect of levosimendan in cardiac surgery, a reduction in the rate of acute renal failure was seen in favor of levosimendan treated patients (odds ratio 0.26 [96 % CI 0.12-0.60], $p = 0.002$, with 228 patients included) (53). Interestingly study was just started on the effect of Levosimendan in Acute Kidney Injury (LAKIS, NCT01720030).

Severe renal failure is a contraindication for levosimendan use as no formal pharmacokinetic studies in heart failure patients with severe renal failure have been conducted. However, many heart failure patients in large regulatory studies such

as REVIVE and SURVIVE had severe renal failure (22, 23, 26). According to pharmacokinetic study in severe renal impairment, the elimination of the levosimendan metabolites was prolonged. The results suggest that if levosimendan was given to heart failure patients with severe renal impairment, the dose should be reduced (54).

Effects on other organs

Some reports on a positive effect of levosimendan on splanchnic (55), liver (56, 57), and diaphragm functions (58) have been published. It must be highlighted, however, that these data were not collected in an AHF population, but in other settings, such as septic shock, cardiac surgery, or chronic obstructive pulmonary disease (COPD).

Adverse events

Levosimendan infusion has generally been well tolerated in the AHF population, despite the high-risk nature of these patients. Hypotension was seen more frequently with levosimendan than with placebo (22), but not when levosimendan was compared with dobutamine (23). Levosimendan has been associated with a higher incidence of atrial fibrillation compared both with placebo (22) and with dobutamine (23). However, conflicting results have been presented with regard to ventricular arrhythmias. In REVIVE a higher incidence of ventricular tachycardia was observed with levosimendan compared with placebo (22). In SURVIVE, ventricular tachycardia was observed with similar frequency in the levosimendan and dobutamine groups (23). In both studies, cardiac failure as an adverse event was less frequent in levosimendan arm, although the result was statistically significant only in SURVIVE.

Safety laboratory values

The changes in safety laboratory variables have been modest in levosimendan studies. A decrease in potassium levels has been seen with levosimendan more often than with comparators (19). Clinically insignificant decreases in haemoglobin and erythrocyte counts have been observed (19).

CLINICAL TRIALS SETTINGS OTHER THAN ADHF

During the past years, various independent research groups have described the use of levosimendan in a range of clinical situations other than ADHF, *e.g.* advanced chronic heart failure, cardiogenic- and septic-shock, cardiac- and non-cardiac surgery, etc. Hereby we review the most recent literature.

Advanced chronic heart failure

Patients with refractory heart failure are hospitalised frequently for clinical deterioration. During such admissions, they often receive infusions of positive inotropes (dobutamine, dopamine, or milrinone) and vasodilators in an effort to improve cardiac performance, facilitate diuresis and promote clinical stability (59). Despite favourable haemodynamic and symptomatic improvement in small clinical studies, concerns have been raised about the safety of intermittent or continuous inotropic therapy. Both dobutamine and milrinone increase the myocardial oxygen demand and intracellular calcium concentration, thus increasing the risk of arrhythmic events and, possibly, death (60, 61). A number of small-scale investigator-initiated studies, in which levosimendan has been administered repeatedly to patients with advanced chronic heart failure, have been reported and are summarized below. In general, the results suggest that levosimendan improves haemodynamics, neurohormones and clinical outcomes. However, the optimal dosing scheme has not been established.

Nanas et al. (62) exposed 36 consecutive patients with NYHA class IV heart failure, resistant to a 24 h continuous infusion of dobutamine: a group was exposed to continuous infusion of dobutamine 10 mg/kg/min for at least 48 h, followed by weekly (or more often if needed) intermittent dobutamine infusions of 8 h ($n = 18$) while the second group, after the initial 24 h infusion of dobutamine, to a 24 h infusion of levosimendan (0.2 mg/kg/min) followed by further biweekly 24 h infusions at the same dose. The addition of intermittent levosimendan infusions was associated with a prolonged survival (45-day survival of 6% vs 61%; $p = 0.0002$).

Mavrogeni et al. (63) performed an open-label prospective study in 50 patients with advanced heart failure (NYHA III or IV). Half of the patients received 24 h infusions of levosimendan (0.1-0.2 μg/kg/min after a 6 μg/kg loading dose) given monthly for 6 months in addition to standard of care and half of the patients were treated with standard of care. At the end of the study, the proportion of patients reporting improvement in symptoms of heart failure was larger in the levosimendan group than in the control group (65% vs 20%; $p < 0.01$). After 6 months, the levosimendan group had a significant increase in left ventricular ejection fraction (LVEF) (28 ± 7% vs controls 21 ± 4%; $p = 0.003$). Twenty-four hours Holter-recordings revealed no significant changes in the occurrence of atrial or ventricular arrhythmias between the two groups. Two patients in the levosimendan group died during the 6-month follow-up period, compared with 8 patients in the control group ($p < 0.05$) (63).

Parle et al. (64) reported on 44 consecutive heart failure patients with systolic impairment, who received between 2 and 26 repeated infusions of levosimendan. The bolus dose was omitted in 65% of administrations and the maximum maintenance infusion was 0.2 μg/kg/min in 60% of patients. The interpretation of efficacy and safety is hampered by the absence of a control group. However, a significant drop in BNP levels and NYHA class was observed and overall the infusions were judged to be well-tolerated.

Parissis et al. (65) performed an open-label, randomised, placebo-controlled study in 25 patients with decompensated chronic heart failure. Five 24 h infusions of levosimendan (a bolus of 6 μg/kg/10 min followed by an infusion of 0.1 μg/kg/min) were given to 17 patients in a 3 weeks interval. Levosimendan treatment was accompanied by significant reductions in cardiac end-systolic and end-diastolic dimensions and volume indices ($p < 0.01$ vs baseline). LVEF was significantly enhanced and left ventricular end-systolic wall stress was reduced. Significant reductions in NT-proBNP ($p < 0.01$), high-sensitivity C-reactive protein ($p < 0.01$) and plasma interleukin-6 ($p = 0.05$) were observed in the levosimendan group. The number of patients with a positive troponin T (≥ 0.01 ng/ml) did not differ between the two groups at baseline, but was significantly higher in the placebo-treated group at the final evaluation ($p < 0.05$). In the placebo group, no statistically significant improvements in any of the variables were seen.

The effects of long-term, intermittent treatment of levosimendan, dobutamine, and the combination of levosimendan with dobutamine on outcomes have recently been studied in 63 patients with decompensated end-stage heart failure. Three groups, each of 21 patients, were assigned to dobutamine 10 μg/kg/min, to levosimendan 0.3 μg/kg/min, or to dobutamine 10 μg/kg/min and concomitant levosimendan 0.2 μg/kg/min. The durations of the infusions were 6 h, and the drugs were given weekly for 6 months. In addition, all patients received oral amiodarone (400 mg/day). The

6-month survival was 80 % in the levosimendan-only group, 48 % in the dobutamine-only group and 43 % in the combined group. Cardiac index was significantly increased and pulmonary capillary wedge pressure significantly decreased only in the levosimendan group (66).

Moreover, a study was conducted in 28 patients with pulmonary hypertension of various etiologies (including secondary to left-sided heart failure) (67). Patients were randomised 2:1 to levosimendan and placebo and they received in total five infusions. The initial 24 h levosimendan infusion (12 μg/kg bolus followed by the maintenance infusion of 0.1-0.2 μg/kg/min) produced a significant decrease in pulmonary vascular resistance. Thereafter, levosimendan was administered every 2 weeks as a 6-h infusion with the infusion rate of 0.2 μg/kg/min. These repeated administrations were found to be safe and the effect on pulmonary vascular resistance was maintained throughout the course of treatment.

Finally, the largest study with repetitive dosing with levosimendan is the LevoRep (Randomised trial investigating the efficacy and safety of pulsed infusions of levosimendan in outpatients with advanced heart failure) study (31), a randomised, double-blind, placebo-controlled study in advanced chronic heart failure. Levosimendan was administered as 6-h infusions (0.2 μg/kg/min) every 2 weeks for 8 weeks (four infusions per patient). Publication of the final results of LevoRep is awaited. Meanwhile, three similar studies has been started: the Intermittent Intravenous Levosimendan in Ambulatory Advanced Chronic Heart Failure Patients study (LION-HEART, NCT01536132), the Randomized, Double-Blind, Placebo Controlled, Multicenter Trial to Study Efficacy, Security, and Long Term Effects of Intermittent Repeated Levosimendan Administration in Patients with Advanced Heart Failure (LAICA, NCT00988806), and the Early LEvosimendanVs Usual Care in Advanced Chronic hearTfailurE (ELEVATE, NCT01290146).

Right ventricular failure

Right ventricular failure is most commonly related to left ventricular heart failure. Biventricular failure has a worse outcome than pure left ventricular failure. In isolated right ventricular failure there is low output syndrome in the absence of pulmonary congestion, with increased jugular venous pressure, with or without hepatic congestion, and a low left ventricular filling pressure. Right ventricular failure can be caused by myocardial ischemia, volume overload and/or pressure overload (68). Investigator initiated studies have been performed in patients with right ventricular failure. In these studies, levosimendan has been shown to:

1) reduce the increased right ventricular afterload;
2) improve right ventricular contractility;
3) improve diastolic function of the right ventricle.

Parissis et al. (69) reported that, in a placebo-controlled study in 54 patients with advanced right ventricular heart failure (NYHA III-IV, LVEF < 35 %), levosimendan (0.1-0.2 μg/kg/min for 24 h) improved Doppler echocardiographic markers of systolic and diastolic right ventricular function. Poelzl et al. (70) administered open-label levosimendan (bolus in the range of 6-12 μg/kg and infusion in the range of 0.075-0.2 μg/kg/min for 24 h) to 18 patients with AHF (characterized by LVEF ≤30 %, cardiac index ≤2.5 l/min/m^2, right atrial pressure ≥10 mmHg, pulmonary capillary wedge pressure ≥15 mmHg) and observed improved right ventricular contractility but not any change in right ventricular afterload.

Russ et al. (71) evaluated right ventricular

function in 25 consecutive acute myocardial infarction patients with cardiogenic shock not responding sufficiently to conventional treatment. A 24 h levosimendan infusion (12 μg/kg bolus in 10 min, followed by a dose of 0.1-0.2 μg/kg/ min) decreased pulmonary vascular resistance and improved cardiac power index (both right and left ventricles), indicating decreased right ventricular afterload and improved right ventricular contractility.

Morelli et al. (72) studied 35 mechanically ventilated patients with acute respiratory distress syndrome (ARDS) related to septic shock. Patients were treated with a 24 h infusion of levosimendan (0.2 μg/kg/min, n = 18) or placebo (n = 17). Reductions in pulmonary vascular resistance and mean pulmonary arterial pressure, and improvements in cardiac index, right ventricular ejection fraction and mixed venous oxygen saturation were observed only in the levosimendan group.

Cardiogenic shock

Cardiogenic shock is a rare but often fatal complication of acute coronary syndrome. The underlying pathophysiology is profound depression of myocardial contractility and the state can be defined as decreased cardiac output and evidence of tissue hypoxia in the presence of adequate intravascular volume (73). The standard of care consists of primary percutaneous coronary intervention for ST-elevated myocardial infarction, fluid therapy, vasopressors and inotropes (74). The role of intra-aortic balloon pump (IABP) counter-pulsation has recently been challenged (75). Data describing the use of levosimendan in cardiogenic shock are still scarce. Nevertheless, the drug appears to be safe and to improve some haemodynamic and ventricular indices (69, 76-78). The improved survival reported by Fuhrmann et al. (79) is notable (30 day survival 69 % with levosimendan vs 37 % with enoximone; p = 0.023, n = 32), but the current dataset is too small to draw definitive conclusions.

Septic shock

Sepsis and septic shock are among the leading causes of death in intensive care units (ICUs) with associated mortality rates up to ~ 50 % (80). Sepsis frequently causes myocardial depression of both ventricles via an impaired response of beta-receptors to endogenous and exogenous catecholamines and via diminished sensitivity of contractile myofilaments to calcium. The results of the few investigator-initiated studies with levosimendan in septic shock support the possibility that levosimendan may have some beneficial effects in this highly vulnerable patient population.

Morelli et al. (81) randomly exposed 28 septic patients with persisting left ventricular dysfunction after 48 h of conventional treatment to receive a 24 h infusion of either levosimendan (0.2 μg/kg/min, n = 15) or dobutamine (5 μg/kg/min, n = 13). In addition to improved haemodynamics, levosimendan increased gastric mucosal flow, creatinine clearance and urinary output and decreased lactate levels, without negatively affecting mean arterial pressure. Reports by the same author (72) of favourable effects of levosimendan in patients with sepsis-related ARDS have already been noted in this review (see section on "Right ventricular failure"). A 500-patient study sponsored by the NIHR-EME program is shortly to commence in the UK (led by Dr. A.C. Gordon in conjunction with the Imperial Clinical Trials Unit) assessing the role of Levosimendan for the Prevention of Acute oRgan Dysfunction in Sepsis (LeoP-ARDS, ISRCTN12776039). This double-blind randomised placebo-controlled trial will test if levosimendan, when added to standard of care, reduces multiple organ failure and improve patient outcome.

Weaning from ventilator

Acquired diaphragm muscle weakness is a key feature in several chronic conditions, including COPD and congestive heart failure, and patients who are difficult to wean from mechanical ventilation (82). About 10-20 % of intubated patients in ICUs are difficult to wean from mechanical ventilation, resulting in increased morbidity, mortality and health care costs (83).

The pathophysiology of muscle weakness in these patients is complex, but includes muscle fiber atrophy and reduced calcium sensitivity of the contractile proteins (84). As respiratory muscle troponin resembles cardiac troponin, it is plausible that levosimendan may enhance contractility in the same way it enhances cardiac contractility. This supposition has support from *in vitro* data (58), experimental observations (85), and a healthy volunteer study (82). Positive effects were seen both in slow and rapid diaphragm muscle fibers (58, 85).

Mechanical ventilation results in rapid loss of diaphragmatic force production (86). In addition, shifting from mechanical ventilation to spontaneous ventilation may dramatically increase left ventricular filling pressure and pulmonary artery pressure, especially in patients with pre-existing cardiac and or pulmonary comorbidities.

Levosimendan was compared to dobutamine in difficult-to-wean COPD patients (87). Levosimendan resulted in significantly greater inhibition of spontaneous ventilation induced increase in pulmonary artery occlusion pressure. Similarly, mean pulmonary artery pressure increased to a lesser extent with levosimendan than with dobutamine. In a prospective observational study in ventilator-dependent difficult-to-wean ICU-patients with diminished left ventricular function (LVEF < 40 %), levosimendan improved cardiac contractility and oxygenation variables and increased the likelihood of separation from mechanical ventilation (83). A study on the Effects of Levosimendan on Diaphragm Function in Mechanically Ventilated Patients (NCT01721434) run at the University Medical Center Nijmegen is currently recruiting.

Cardiac surgery

Peri-operative acute cardiovascular dysfunction occurs in more than 20 % of patients undergoing cardiac surgery; yet current AHF classification (68) is not applicable to this period. Indicators of major perioperative risk include unstable coronary syndromes, decompensated heart failure, significant arrhythmias and valvular disease. Clinical risk factors include history of heart disease, including heart failure, cerebrovascular disease, presence of diabetes mellitus, renal insufficiency and high-risk surgery (88).

Preserving heart function during cardiac surgery is a major goal. However, optimal perioperative use of inotropes and vasopressors in cardiac surgery remains controversial. Neither is the use of an IABP or left ventricular assist device (LVAD) risk-free (89, 90). The comparative data on levosimendan in this situation suggest that it has the potential to become a drug of choice among the agents with inotropic properties, possibly due to its cardioprotective qualities.

Several studies have demonstrated that levosimendan protects the myocardium and improves tissue perfusion, while minimising tissue damage during the cardiac surgery and reperfusion periods (20, 33, 91). Current data from individual studies and meta-analyses suggest that levosimendan is superior to traditional inotropes (dobutamine, phosphodiesterase-inhibitors), delivering sustained haemodynamic improvement, diminished myocardial injury, and better outcomes (92, 93).

Tritapepe et al. (94) performed a ran-

domised, double-blind, placebo-controlled study in 106 patients undergoing elective multivesselcoronary artery bypass grafting (CABG). Levosimendan (bolus only, 24 μg/kg over 10 min), or placebo was given before initiation of cardiopulmonary bypass (CPB). Mean tracheal intubation time and length of ICU stay were significantly shorter in the levosimendan group (both $p < 0.01$) and the number of patients needing inotropic support for > 12 h was significantly lower with levosimendan (18.0 % vs 3.8 %; $p = 0.021$). Significantly higher postoperative values of mean arterial pressure, cardiac index and cardiac power index, and a lower systemic vascular resistance index were observed with levosimendan, while troponin I increases were significantly smaller (all $p < 0.005$ or less).

In a placebo-controlled study in 60 patients undergoing CABG Eriksson et al. showed that levosimendan (0.2 μg/kg/min, 24 h) increases the success of primary weaning from CPB (73 % vs 33 %, $p = 0.002$) (33).

Lahtinen et al. (95) reported a randomised, double-blind, placebo-controlled study in 200 patients assigned to undergo heart valve or combined heart valve and CABG surgery. Levosimendan was given as a 24-h infusion started at the induction of anaesthesia with a 24 μg/kg bolus over 30 min and thereafter at a dose of 0.2 μg/kg/min. The primary outcome measure was heart failure, defined as cardiac index < 2.0 l/min/m^2 or failure to wean from CPB necessitating inotrope administration for at least 2 hours postoperatively after CPB. Heart failure was less frequent in the levosimendan group than in the placebo group (15 % vs 58 %; $p < 0.001$). Need of inotrope use for rescue was also lower in the levosimendan group (risk ratio 0.11; 95 % CI 0.01-0.89), and IABP was utilised in one patient (1 %) in the levosimendan versus nine (9 %) in the placebo group (risk ratio 0.11; 95 % CI 0.01-0.87). Creatine kinase was lower in the levosimendan group on the first post-operative day ($p = 0.011$). The levosimendan group had more hypotension and needed norepinephrine more often (83 vs 52, $p < 0.001$). There was no difference in in-hospital or 6-month mortality (overall, 12 % of the patients died in both groups).

The meta-analysis by Landoni et al. (40) on mortality with intravenous levosimendan identified 17 studies in cardiac surgery, including 1233 patients. Levosimendan reduced mortality significantly in cardiac surgery patients compared with the control arms (5.8 % vs 12.9 %; risk ratio 0.52, 95 % CI 0.35-0.76).

In another independent meta-analysis, Maharaj and Metaxa (41) reported a favourable effects of levosimendan on cardiac index (mean difference 1.63, 95 % CI 1.43-1.83, $p < 0.00001$), length of ICU stay (mean difference -26 hours 95 % CI -46 to -6, $p = 0.01$), rate of atrial fibrillation (odds ratio 0.54, 95 % CI 0.36-0.82, $p = 0.004$), and troponin I levels (mean difference -1.59, 95 % CI 1.78-1.40, $p < 0.00001$) as well as a mortality reduction after coronary revascularisation (odds ratio 0.40, 95 % CI 0.21-0.76, $p = 0.005$). These data amplified the findings of previous meta-analyses (42,44,53).

Recently, a group of experts published a consensus report on how to use levosimendan in cardiac surgery (30) and the study Levosimendan in High Risk Patients Undergoing Cardiac Surgery (HSR-LEVO, NCT00994825) was initiated and is currently recruiting. Of interest also two recent papers on reduction of perioperative mortality (96, 97) in which levosimendan is cited as a drug with potential to reduce mortality in surgical settings.

Non cardiac surgery

Congestive heart failure is a non-uncommon co-morbidity in patients undergoing

non-cardiac surgery, and is strongly associated with a doubling of the in-hospital mortality (98). Some authors have suggested a role for levosimendan in the preoperative optimization of cardiac function in patient undergoing major elective non-cardiac surgery (99). Katsaragakis et al. reported on the use of levosimendan in high risk patients undergoing abdominal surgery (100), while Ponschab et al. (101) described how levosimendan infusion improves haemodynamics in elderly heart failure patients undergoing urgent hip fracture repair. Both groups demonstrated that the administration of levosimendan was safe and observed improvements in ejection fraction, echochardiographic parameters as well as a range of haemodynamic indices both intra- and postoperatively. Therefore, Morelli et al. suggested that the prophylactic administration of levosimendan in patients with compromised myocardial physiologic reserve, undergoing anesthesia and major non-cardiac surgery, is safe and advisable for preoperative cardiac optimization (99).

Paediatric use

In the paediatric cardiac settings, inotropic support is often employed on the basis of extrapolations from adult studies, the underlying pathophysiology, the pharmacodynamics of inotropes, and anecdotal experience. There are currently no official indications for levosimendan in patients under 18 years of age (see levosimendan SPC), but the drug has been indeed studied and used as a rescue drug in the paediatric ICU (PICU) and in the operating room. The published paediatric experience in levosimendan comprises mainly observational studies [see recent reviews by Hoffman (102) and by Angadi et al. (103)] or analyses of patient registers (104), but also four randomised and blinded trials have been reported (105-108). All in all, 645 patients were included in 14 reports.

The pharmacokinetic profile of levosimendan in children with congenital heart disease is similar to that in adult patients with congestive heart failure (109). Ten hours after the initiation of 48 hours levosimendan infusion in neonates undergoing cardiac surgery, the active metabolite OR-1896 was detectable in plasma and remained measurable up to 14 days (106). This observation suggests that levosimendan will exert prolonged hemodynamic effects in neonates after cessation of infusion similar to those noted in adults.

As it regards the doses, levosimendan has been administered in children without or with a bolus dose of 6-24 mcg/kg, and by infusion of 0.05 to 0.2 mcg/kg/min similarly to adults. Levosimendan infusions have been well tolerated in children with acute heart failure or children who are undergoing cardiac surgery; only transient hypotension or tachycardia has been reported in the beginning of the infusion. The largest published data in paediatrics included retrospectively-gathered data on 484 levosimendan infusions delivered to 293 patients at a single PICU (104). A majority of the patients (65 %) were aged 12 months or younger. Most of the physicians surveyed (89 %) thought that levosimendan postponed or reduced the need for mechanical cardiac support in children with cardiomyopathy or who were undergoing cardiac surgery. Levosimendan was shown to be as efficacious as milrinone with comparable hemodynamic data in two randomised and double-blind studies in children and in neonates undergoing cardiac surgery (107, 110). In another comparison of milrinone and levosimendan in neonates undergoing cardiac surgery, levosimendan group had higher pH, lower blood glucose level and lower inotrope score in the PICU (106).

Finally, in a randomised double-blind study in children younger than 4 years of age undergoing cardiac surgery, patients receiv-

ing levosimendan had significantly higher cardiac index and lower pulmonary artery pressure than children receiving dobutamine (108). Of interest is a report describing a strategy for rotating inotropes in pediatric decompensated heart failure (111).

Other clinical settings

Case reports, uncontrolled small series or small-scale comparative studies with levosimendan have been published *e.g.* in calcium-channels-blockers intoxication (112) and Takotsubo cardiomyopathy (113, 114).

CONCLUSION, GUIDANCE FOR CLINICAL USE, FUTURE DEVELOPMENTS

Its pharmacologic and pharmacodynamic properties differentiate levosimendan from other inotropes. The infusion of levosimendan has consistently been shown to enhance left ventricular performance and to decrease left ventricular filling pressure and plasma BNP concentrations without increasing myocardial oxygen consumption (*Table 2*). Neither age nor gender influence the responses to levosimendan. Following a 24 h infusion of levosimendan, the active metabolite reaches pharmacologically active plasma levels, resulting in a prolonged haemodynamic effect (115, 116), wich persists for at least 7 days (24). The haemodynamic and neurohumoral improvement is associated with a symptomatic benefit that is sustained and superior to that of placebo. In contrast to dobutamine, the effects of levosimendan are not attenuated with concomitant beta-blocker use (26). In two early phase III studies, a significant mortality benefit with levosimendan was observed in comparison with both placebo (RUSSLAN) (34) and dobutamine (LIDO) (17). These favourable results were not, however, corroborated by two subsequent studies where levosimendan was compared with placebo (REVIVE) (35) and dobutamine (SURVIVE) (23).

Table 2 - *Clinical effects of levosimendan.*

Haemodynamic and neurohormonal effects	Other clinical effects
Pulmonary capillary wedge pressure ↓↓↓	Relief of symptoms of heart failure
Cardiac output (index) ↑↑	Effects maintained also with beta-blockers
Stroke volume ↑	Sustained effects due to an active metabolite
Systemic vascular resistance ↓↓	No development of tolerance
Pulmonary vascular resistance ↓↓	No increase in myocardial oxygen consumption
Natriuretic peptide levels ↓↓↓	Anti-ischemic effect
	No impairment of diastolic function
↓ = decrease, ↑ = increase	

Subgroup analyses from the SURVIVE study indicate nevertheless that levosimendan outperforms dobutamine in betablocked patients and in patients with acute decompensation of an existing chronic failure (26). Recent independent meta-analyses on the effect of levosimendan on mortality suggest a survival benefit of levosimendan both compared to placebo and dobutamine; a trend towards a more favourable outcome effect was noted with lower levosimendan doses (≤ 0.1 μg/kg/min) (40). Dosing guidance for levosimendan in ADHF (*Table 3*) may be proposed from the experience of controlled trials. Levosimendan infusion has generally been well tolerated.

Data from the REVIVE and SURVIVE studies - the two largest studies conducted to date - indicate that hypotension was more frequent with levosimendan than with placebo, though not dobutamine. Levosimen-

Table 3 - *Dosing guidance for levosimendan in ADHF.*

- Loading dose (6-12 µg/kg over 10 min) only if immediate effect needed and systolic blood pressure > 100 mmHg.
- Maintenance infusion rate 0.05-0.2 µg/kg/min with individualised dosing regimen.
- Infusion duration up to 24 hours.
- Hypovolaemia to be avoided before and during the treatment (fluid as needed; intravenous diuretics with caution).
- Hypokalemia to be avoided.

ADHF = acutely decompensated heart failure.

dan was also associated with higher incidence of atrial fibrillation relative to both those comparators.

It should be recalled that, in addition to contractility increasing effects, levosimendan has profound vasodilatory effects. Clinical studies have indicated that levosimendan should be given cautiously to patients with low blood pressure, especially in case of hypovolaemia.

Use of lower infusion rates without the loading bolus should be considered for such patients. In case of unintended overdose, pronounced haemodynamic effects would be expected; mainly hypotension and increased heart rate/arrhythmias. Hypotension should be treated with fluid resuscitation and vasoconstrictors, as needed. Arrhythmias may be treated with intravenous beta-blockade or amiodarone (if blood pressure allows). Due to the formation of the active metabolite, the follow-up may need to be prolonged, if the total dose of parent drug is substantial. Applications of this drug in fields such as cardiac and non-cardiac surgery, cardiogenic- and septic-shock, and others have been proposed.

The effects of levosimendan in these settings have been described in many independent studies, and there is a strong rationale for suitably powered studies to corroborate those reports. Positive experience in a range of niche applications has also been documented.

REFERENCES

1. Pöss J, Link A, Böhm M. Pharmacological Treatment of Acute Heart Failure: Current Treatment and New Targets. Clin Pharmacol Ther. 2013; 94: 499-508.
2. Hasenfuss G, Teerlink JR. Cardiac inotropes: current agents and future directions. Eur Heart J 2011; 32: 1838-45.
3. Pollesello P, Papp Z, Nieminen MS. Lessons from Lisbon on AHF drug treatment: Is it really true that all-old-failed-all-new-will-succeed? Int J Cardiol 2013. Epub ahead of print. PMID: 23886529.
4. Haikala H, Kaivola J, Nissinen E, Wall P, Levijoki J, Linden IB. Cardiac troponin C as a target protein for a novel calcium sensitizing drug, levosimendan. J Mol Cell Cardiol 1995; 27: 1859-66.
5. Haikala H, Linden IB. Mechanisms of action of calcium-sensitizing drugs. J Cardiovasc Pharmacol 1995; 26: 10-9.
6. Pollesello P, Ovaska M, Kaivola J, Tilgmann C, Lundstrom K, Kalkkinen N, et al. Binding of a new Ca2 + sensitizer, levosimendan, to recombinant human cardiac troponin C. A molecular modelling, fluorescence probe, and proton nuclear magnetic resonance study. J Biol Chem 1994; 269: 28584-90.
7. Sorsa T, Pollesello P, Solaro RJ. The contractile apparatus as a target for drugs against heart failure: interaction of levosimendan, a calcium sensitiser, with cardiac troponin c. Mol Cell Biochem 2004; 266: 87-107.
8. Haikala H, Pollesello P. Calcium sensitivity enhancers. IDrugs 2000; 3: 1199-205.
9. Yokoshiki H, Katsube Y, Sunagawa M, Sperelakis N. Levosimendan, a novel Ca2 + sensitizer, activates the glibenclamide-sensitive K + channel in rat arterial myocytes. Eur J Pharmacol 1997; 333: 249-59.
10. Pataricza J, Hohn J, Petri A, Balogh A, Papp JG. Comparison of the vasorelaxing effect of cromakalim and the new inodilator, levosimendan, in human isolated portal vein. J Pharm Pharmacol 2000; 52: 213-7.
11. Kaheinen P, Pollesello P, Levijoki J, Haikala H. Levosimendan increases diastolic coronary flow in isolated guinea-pig heart by opening ATP-sensitive potassium channels. J Cardiovasc Pharmacol 2001; 37: 367-74.
12. Erdei N, Papp Z, Pollesello P, Edes I, Bagi Z. The levosimendan metabolite OR-1896 elicits vasodilation by activating the K(ATP) and BK(Ca) channels in rat isolated arterioles. Br J Pharmacol 2006; 148: 696-702.
13. Maytin M, Colucci WS. Cardioprotection: a new paradigm in the management of acute heart failure syndromes. Am J Cardiol 2005; 96: 26-31.
14. Louhelainen M, Vahtola E, Kaheinen P, Leskinen H, Merasto S, Kyto V, et al. Effects of levosimendan on cardiac remodeling and cardiomyocyte apoptosis in hypertensive Dahl/Rapp rats. Br J Pharmacol 2007; 150: 851-61.
15. Pollesello P, Papp Z. The cardioprotective effects of levosimendan: preclinical and clinical evidence. J Cardiovasc Pharmacol 2007; 50: 257-63.
16. du Toit EF, Genis A, Opie LH, Pollesello P, Lochner A. A role for the RISK pathway and K(ATP) channels in pre- and post-conditioning induced by levosimendan in the isolated guinea pig heart. Br J Pharmacol 2008; 154: 41-50.
17. Follath F, Cleland JG, Just H, Papp JG, Scholz H, Peuhkurinen K, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. Lancet 2002; 360: 196-202.
18. Slawsky MT, Colucci WS, Gottlieb SS, Greenberg BH,

Haeusslein E, Hare J, et al. Acute hemodynamic and clinical effects of levosimendan in patients with severe heart failure. Study Investigators. Circulation 2000; 102: 2222-7.
19. Nieminen MS, Akkila J, Hasenfuss G, Kleber FX, Lehtonen LA, Mitrovic V, et al. Hemodynamic and neurohumoral effects of continuous infusion of levosimendan in patients with congestive heart failure. J Am Coll Cardiol 2000; 36: 1903-12.
20. Lilleberg J, Nieminen MS, Akkila J, Heikkila L, Kuitunen A, Lehtonen L, et al. Effects of a new calcium sensitizer, levosimendan, on haemodynamics, coronary blood flow and myocardial substrate utilization early after coronary artery bypass grafting. Eur Heart J 1998; 19: 660-8.
21. Ukkonen H, Saraste M, Akkila J, Knuuti J, Karanko M, Iida H, et al. Myocardial efficiency during levosimendan infusion in congestive heart failure. Clin Pharmacol Ther 2000; 68: 522-31.
22. Packer M, Colucci W, Fisher L, Massie BM, Teerlink JR, Young J, et al. Effect of Levosimendan on the Short-Term Clinical Course of Patients With Acutely Decompensated Heart Failure. JCHF 2013; 1: 103-11.
23. Mebazaa A, Nieminen MS, Packer M, Cohen-Solal A, Kleber FX, Pocock SJ, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. JAMA 2007; 297: 1883-91.
24. Lilleberg J, Laine M, Palkama T, Kivikko M, Pohjanjousi P, Kupari M. Duration of the haemodynamic action of a 24-h infusion of levosimendan in patients with congestive heart failure. Eur J Heart Fail 2007; 9: 75-82.
25. Kivikko M, Lehtonen L, Colucci WS. Sustained hemodynamic effects of intravenous levosimendan. Circulation 2003; 107: 81-6.
26. Mebazaa A, Nieminen MS, Filippatos GS, Cleland JG, Salon JE, Thakkar R, et al. Levosimendan vs. dobutamine: outcomes for acute heart failure patients on beta-blockers in SURVIVE. Eur J Heart Fail 2009; 11: 304-11.
27. Sonntag S, Sundberg S, Lehtonen LA, Kleber FX. The calcium sensitizer levosimendan improves the function of stunned myocardium after percutaneous transluminal coronary angioplasty in acute myocardial ischemia. J Am Coll Cardiol 2004; 43: 2177-82.
28. Givertz MM, Andreou C, Conrad CH, Colucci WS. Direct myocardial effects of levosimendan in humans with left ventricular dysfunction: alteration of force-frequency and relaxation-frequency relationships. Circulation 2007; 115: 1218-24.
29. Papp Z, Edes I, Fruhwald S, De Hert SG, Salmenpera M, Leppikangas H, et al. Levosimendan: molecular mechanisms and clinical implications: consensus of experts on the mechanisms of action of levosimendan. Int J Cardiol 2012; 159: 82-7.
30. Toller W, Algotsson L, Guarracino F, Hormann C, Knotzer J, Lehmann A, et al. Perioperative use of levosimendan: best practice in operative settings. J Cardiothorac Vasc Anesth 2013; 27: 361-6.
31. Altenberger J, Parissis JT, Ulmer H, Poelzl G. Rationale and design of the multicentre randomized trial investigating the efficacy and safety of pulsed infusions of levosimendan in outpatients with advanced heart failure (LevoRep study). Eur J Heart Fail 2010; 12: 186-92.
32. Salmenpera M, Eriksson H. Levosimendan in perioperative and critical care patients. Curr Opin Anaesthesiol 2009; 22: 496-501.
33. Eriksson HI, Jalonen JR, Heikkinen LO, Kivikko M, Laine M, Leino KA, et al. Levosimendan facilitates weaning from cardiopulmonary bypass in patients undergoing coronary artery bypass grafting with impaired left ventricular function. Ann Thorac Surg 2009; 87: 448-54.
34. Moiseyev VS, Poder P, Andrejevs N, Ruda MY, Golikov AP, Lazebnik LB, et al. Safety and efficacy of a novel calcium sensitizer, levosimendan, in patients with left ventricular failure due to an acute myocardial infarction. A randomized, placebo-controlled, double-blind study (RUSSLAN). Eur Heart J 2002; 23: 1422-32.
35. Packer M, Colucci WS, Fisher L, Massie BM, Teerlink JR, Young JB, et al. Development of a comprehensive new endpoint for the evaluation of new treatments for acute decompensated heart failure: results with levosimendan in the REVIVE 1 study. J Card Fail: Abstracts From the 7th Annual Scientific Meeting of the Heart Failure Society of America 2003; 9: 61.
36. Lilleberg J, Sundberg S, Nieminen MS. Dose-range study of a new calcium sensitizer, levosimendan, in patients with left ventricular dysfunction. J Cardiovasc Pharmacol 1995; 26: 63-9.
37. Bergh CH, Andersson B, Dahlstrom U, Forfang K, Kivikko M, Sarapohja T, et al. Intravenous levosimendan vs. dobutamine in acute decompensated heart failure patients on beta-blockers. Eur J Heart Fail 2010; 12: 404-10.
38. de Lissovoy G, Fraeman K, Teerlink JR, Mullahy J, Salon J, Sterz R, et al. Hospital costs for treatment of acute heart failure: economic analysis of the REVIVE II study. Eur J Health Econ 2010; 11: 185-93.
39. Delaney A, Bradford C, McCaffrey J, Bagshaw SM, Lee R. Levosimendan for the treatment of acute severe heart failure: a meta-analysis of randomised controlled trials. Int J Cardiol 2010; 138: 281-9.
40. Landoni G, Biondi-Zoccai G, Greco M, Greco T, Bignami E, Morelli A, et al. Effects of levosimendan on mortality and hospitalization. A meta-analysis of randomized controlled studies. Crit Care Med 2012; 40: 634-46.
41. Maharaj R, Metaxa V. Levosimendan and mortality after coronary revascularisation: a meta-analysis of randomised controlled trials. Crit Care 2011; 15: 140.
42. Zangrillo A, Biondi-Zoccai G, Mizzi A, Bruno G, Bignami E, Gerli C, et al. Levosimendan reduces cardiac troponin release after cardiac surgery: a meta-analysis of randomized controlled studies. J Cardiothorac Vasc Anesth 2009; 23: 474-8.
43. Huang X, Lei S, Zhu MF, Jiang RL, Huang LQ, Xia GL, et al. Levosimendan versus dobutamine in critically ill patients: a meta-analysis of randomized controlled trials. J Zhejiang Univ Sci B 2013; 14: 400-15.
44. Harrison RW, Hasselblad V, Mehta RH, Levin R, Harrington RA, Alexander JH. Effect of Levosimendan on Survival and Adverse Events After Cardiac Surgery: A Meta-analysis. J Cardiothorac Vasc Anesth 2013.
45. Mebazaa A, Parissis J, Porcher R, Gayat E, Nikolaou M, Boas FV, et al. Short-term survival by treatment among patients hospitalized with acute heart failure: the global ALARM-HF registry using propensity scoring methods. Intensive Care Med 2011; 37: 290-301.
46. Fedele F, D'Ambrosi A, Bruno N, Caira C, Brasolin B, Mancone M. Cost-effectiveness of levosimendan in patients with acute heart failure. J Cardiovasc Pharmacol 2011; 58: 363-6.
47. Zemljic G, Bunc M, Yazdanbakhsh AP, Vrtovec B. Levosimendan improves renal function in patients with advanced chronic heart failure awaiting cardiac transplantation. J Card Fail 2007; 13: 417-21.
48. Silva-Cardoso J, Ferreira J, Oliveira-Soares A, Martins-de-Campos J, Fonseca C, Lousada N, et al. Effectiveness and safety of levosimendan in clinical practice. Rev Port Cardiol 2009; 28: 143-54.

49. Yilmaz MB, Yalta K, Yontar C, Karadas F, Erdem A, Turgut OO, et al. Levosimendan improves renal function in patients with acute decompensated heart failure: comparison with dobutamine. Cardiovasc Drugs Ther 2007; 21: 431-5.
50. Hou Z-Q, Sun Z-X, Su C-Y, Tan H, Zhong X, Hu B, et al. Effect of Levosimendan on Estimated Glomerular Filtration Rate in Hospitalized Patients with Decompensated Heart Failure and Renal Dysfunction. Cardiovascular Therapeutics 2013; 31: 108-14.
51. Bragadottir G, Redfors B, Ricksten SE. Effects of Levosimendan on Glomerular Filtration Rate, Renal Blood Flow, and Renal Oxygenation After Cardiac Surgery With Cardiopulmonary Bypass: A Randomized Placebo-Controlled Study. Crit Care Med. 2013; 41: 2328-35.
52. Yilmaz MB, Grossini E, Silva Cardoso JC, Edes I, Fedele F, Pollesello P, et al. Renal Effects of Levosimendan: A Consensus Report. Cardiovasc Drugs Ther 2013. Epub ahead of print. PMID: 23929366.
53. Landoni G, Mizzi A, Biondi-Zoccai G, Bruno G, Bignami E, Corno L, et al. Reducing mortality in cardiac surgery with levosimendan: a meta-analysis of randomized controlled trials. J Cardiothorac Vasc Anesth 2010; 24: 51-7.
54. Puttonen J, Kantele S, Kivikko M, Hakkinen S, Harjola VP, Koskinen P, et al. Effect of severe renal failure and haemodialysis on the pharmacokinetics of levosimendan and its metabolites. Clin Pharmacokinet 2007; 46: 235-46.
55. Morelli A, Donati A, Ertmer C, Rehberg S, Lange M, Orecchioni A, et al. Levosimendan for resuscitating the microcirculation in patients with septic shock: a randomized controlled study. Crit Care 2010; 14: 232.
56. Alvarez J, Baluja A, Selas S, Otero P, Rial M, Veiras S, et al. A comparison of doubutamine and levosimendan n hepatic blood flow in patients with a low cardiac output state after cardiac surgery: a randomised controlled study. Anaesth Intensive Care 2013; 41.
57. Memis D, Inal MT, Sut N. The effects of levosimendan vs dobutamine added to dopamine on liver functions assessed with noninvasive liver function monitoring in patients with septic shock. J Crit Care 2012; 27: 318 1-6.
58. van Hees HW, Dekhuijzen PN, Heunks LM. Levosimendan enhances force generation of diaphragm muscle from patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2009; 179: 41-7.
59. Jessup M, Abraham WT, Casey DE, Feldman AM, Francis GS, Ganiats TG, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. Circulation 2009; 119: 1977-2016.
60. Stevenson LW. Clinical use of inotropic therapy for heart failure: Looking backward or forward? Part II: Chronic inotropic therapy. Circulation 2003; 108: 492-7.
61. Stevenson LW. Clinical use of inotropic therapy for heart failure: Looking backward or forward? Part I: Inotropic infusions during hospitalization. Circulation 2003; 108: 367-72.
62. Nanas JN, Papazoglou P, Tsagalou EP, Ntalianis A, Tsolakis E, Terrovitis JV, et al. Efficacy and safety of intermittent, long-term, concomitant dobutamine and levosimendan infusions in severe heart failure refractory to dobutamine alone. Am J Cardiol 2005; 95: 768-71.
63. Mavrogeni S, Giamouzis G, Papadopoulou E, Thomopoulou S, Dritsas A, Athanasopoulos G, et al. A 6-month follow-up of intermittent levosimendan administration effect on systolic function, specific activity questionnaire, and arrhythmia in advanced heart failure. J Card Fail 2007; 13: 556-9.
64. Parle NM, Thomas MD, Dembo L, Best M, Driscoll GO. Repeated infusions of levosimendan: well tolerated and improves functional capacity in decompensated heart failure - a single-centre experience. Heart Lung Circ 2008; 17: 206-10.
65. Parissis JT, Adamopoulos S, Farmakis D, Filippatos G, Paraskevaidis I, Panou F, et al. Effects of serial levosimendan infusions on left ventricular performance and plasma biomarkers of myocardial injury and neurohormonal and immune activation in patients with advanced heart failure. Heart 2006; 92: 1768-72.
66. Bonios MJ, Terrovitis JV, Drakos SG, Katsaros F, Pantsios C, Nanas SN, et al. Comparison of three different regimens of intermittent inotrope infusions for end stage heart failure. Int J Cardiol 2011; 159: 225-9.
67. Kleber FX, Bollmann T, Borst MM, Costard-Jackle A, Ewert R, Kivikko M, et al. Repetitive dosing of intravenous levosimendan improves pulmonary hemodynamics in patients with pulmonary hypertension: results of a pilot study. J Clin Pharmacol 2009; 49: 109-15.
68. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). Eur Heart J 2008; 29: 2388-442.
69. Parissis JT, Paraskevaidis I, Bistola V, Farmakis D, Panou F, Kourea K, et al. Effects of levosimendan on right ventricular function in patients with advanced heart failure. Am J Cardiol 2006; 98: 1489-92.
70. Poelzl G, Zwick RH, Grander W, Metzler B, Jonetzko P, Frick M, et al. Safety and effectiveness of levosimendan in patients with predominant right heart failure. Herz 2008; 33: 368-73.
71. Russ MA, Prondzinsky R, Carter JM, Schlitt A, Ebelt H, Schmidt H, et al. Right ventricular function in myocardial infarction complicated by cardiogenic shock: Improvement with levosimendan. Crit Care Med 2009; 37: 3017-23.
72. Morelli A, Teboul JL, Maggiore SM, Vieillard-Baron A, Rocco M, Conti G, et al. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: A pilot study. Crit Care Med 2006; 34: 2287-93.
73. Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. Circulation 2008; 117: 686-97.
74. Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012; 33: 2569-619.
75. Thiele H, Zeymer U, Neumann FJ, Ferenc M, Olbrich HG, Hausleiter J, et al. Intraaortic balloon support for myocardial infarction with cardiogenic shock. N Engl J Med 2012; 367: 1287-96.
76. Christoph A, Prondzinsky R, Russ M, Janusch M, Schlitt A, Lemm H, et al. Early and sustained haemodynamic improvement with levosimendan compared to intraaortic balloon counterpulsation (IABP) in cardiogenic shock complicating acute myocardial infarction. Acute Card Care 2008; 10: 49-57.

77. Samimi-Fard S, Garcia-Gonzalez MJ, Dominguez-Rodriguez A, Abreu-Gonzalez P. Effects of levosimendan versus dobutamine on long-term survival of patients with cardiogenic shock after primary coronary angioplasty. Int J Cardiol 2008; 127: 284-7.
78. Berry WT, Hewson RW, Langrish CJ, McKenzie CA, Barrett NA. Levosimendan: A retrospective single-center case series. J Crit Care 2013. Epub ahead of print. PMID: 23998721.
79. Fuhrmann J, Schmeisser A, Schulze MR, Schoen S, Weinbrenner C, Strasser RH. Levosimendan in advanced cardiogenic shock improved survival compared with enoximone. Circulation 2004; 110: 478.
80. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, et al. Sepsis in European intensive care units: results of the SOAP study. Crit Care Med 2006; 34: 344-53.
81. Morelli A, De Castro S, Teboul JL, Singer M, Rocco M, Conti G, et al. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. Intensive Care Med 2005; 31: 638-44.
82. Doorduin J, Sinderby CA, Beck J, Stegeman DF, van Hees HW, van der Hoeven JG, et al. The calcium sensitizer levosimendan improves human diaphragm function. Am J Respir Crit Care Med 2012; 185: 90-5.
83. Sterba M, Banerjee A, Mudaliar Y. Prospective observational study of levosimendan and weaning of difficult-to-wean ventilator dependent intensive care patients. Crit Care Resusc 2008; 10: 182-6.
84. Ottenheijm CAC, Heunks LMA, Sieck GC, Zhan W-Z, Jansen SM, Degens H, et al. Diaphragm Dysfunction in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 2005; 172: 200-5.
85. van Hees HW, Andrade Acuna G, Linkels M, Dekhuijzen PN, Heunks LM. Levosimendan improves calcium sensitivity of diaphragm muscle fibres from a rat model of heart failure. Br J Pharmacol 2011; 162: 566-73.
86. Jaber S, Jung B, Matecki S, Petrof BJ. Clinical review: ventilator-induced diaphragmatic dysfunction--human studies confirm animal model findings! Crit Care 2011; 15: 206.
87. Ouanes-Besbes L, Ouanes I, Dachraoui F, Dimassi S, Mebazaa A, Abroug F. Weaning difficult-to-wean chronic obstructive pulmonary disease patients: A pilot study comparing initial hemodynamic effects of levosimendan and dobutamine. J Crit Care 2011; 26: 15-21.
88. Mebazaa A, Pitsis AA, Rudiger A, Toller W, Longrois D, Ricksten SE, et al. Clinical review: practical recommendations on the management of perioperative heart failure in cardiac surgery. Crit Care 2010; 14: 201.
89. Overwalder PJ. Intra Aortic Balloon Pump (IABP) Counterpulsation mirror with better quality. Internet J Thorac Cardiovasc Surg 1999; 2.
90. Cheng JM, den Uil CA, Hoeks SE, van der Ent M, Jewbali LS, van Domburg RT, et al. Percutaneous left ventricular assist devices vs. intra-aortic balloon pump counterpulsation for treatment of cardiogenic shock: a meta-analysis of controlled trials. Eur Heart J 2009; 30: 2102-8.
91. Nijhawan N, Nicolosi AC, Montgomery MW, Aggarwal A, Pagel PS, Warltier DC. Levosimendan enhances cardiac performance after cardiopulmonary bypass: a prospective, randomized placebo-controlled trial. J Cardiovasc Pharmacol 1999; 34: 219-28.
92. Levin R, Degrange MA, Porcile R, Salvagio F, Blanco N, Botbol AL, et al. [The calcium sensitizer levosimendan gives superior results to dobutamine in postoperative low cardiac output syndrome]. Rev Esp Cardiol 2008; 61: 471-9.
93. De Hert SG, Lorsomradee S, Cromheecke S, Van der Linden PJ. The effects of levosimendan in cardiac surgery patients with poor left ventricular function. Anesth Analg 2007; 104: 766-73.
94. Tritapepe L, De Santis V, Vitale D, Guarracino F, Pellegrini F, Pietropaoli P, et al. Levosimendan pre-treatment improves outcomes in patients undergoing coronary artery bypass graft surgery. Br J Anaesth 2009; 102: 198-204.
95. Lahtinen P, Pitkanen O, Polonen P, Turpeinen A, Kivinieemi V, Uusaro A. Levosimendan reduces heart failure after cardiac surgery: a prospective, randomized, placebo-controlled trial. Crit Care Med 2011; 39: 2263-70.
96. Landoni G, Rodseth RN, Santini F, Ponschab M, Ruggeri L, Szekely A, et al. Randomized evidence for reduction of perioperative mortality. J Cardiothorac Vasc Anesth 2012; 26: 764-72.
97. Landoni G, Augoustides JG, Guarracino F, Santini F, Ponschab M, Pasero D, et al. Mortality reduction in cardiac anesthesia and intensive care: results of the first International Consensus Conference. Acta Anaesthesiol Scand 2011; 55: 259-66.
98. Pearse RM, Moreno RP, Bauer P, Pelosi P, Metnitz P, Spies C, et al. Mortality after surgery in Europe: a 7 day cohort study. Lancet 2012; 380: 1059-65.
99. Morelli A, Ertmer C, Pietropaoli P, Westphal M. Reducing the risk of major elective non-cardiac surgery: is there a role for levosimendan in the preoperative optimization of cardiac function? Curr Drug Targets 2009; 10: 863-71.
100. Katsaragakis S, Kapralou A, Markogiannakis H, Kofinas G, Theodoraki EM, Larentzakis A, et al. Preoperative levosimendan in heart failure patients undergoing noncardiac surgery. Neth J Med 2008; 66: 154-9.
101. Ponschab M, Hochmair N, Ghazwinian N, Mueller T, Plochl W. Levosimendan infusion improves haemodynamics in elderly heart failure patients undergoing urgent hip fracture repair. Eur J Anaesthesiol 2008; 25: 627-33.
102. Hoffman TM. Newer inotropes in pediatric heart failure. J Cardiovasc Pharmacol 2011; 58: 121-5.
103. Angadi U, Westrope C, Chowdhry MF. Is levosimendan effective in paediatric heart failure and post-cardiac surgeries? Interact Cardiovasc Thorac Surg 2013; 17: 710-4.
104. Suominen PK. Single-center experience with levosimendan in children undergoing cardiac surgery and in children with decompensated heart failure. BMC Anesthesiol 2011; 11: 18.
105. Ricci Z, Garisto C, Favia I, Vitale V, Di Chiara L, Cogo PE. Levosimendan infusion in newborns after corrective surgery for congenital heart disease: randomized controlled trial. Intensive Care Med 2012; 38: 1198-204.
106. Pellicer A, Riera J, Lopez-Ortego P, Bravo MC, Madero R, Perez-Rodriguez J, et al. Phase 1 study of two inodilators in neonates undergoing cardiovascular surgery. Pediatr Res 2013; 73: 95-103.
107. Momeni M, Rubay J, Matta A, Rennotte MT, Veyckemans F, Poncelet AJ, et al. Levosimendan in congenital cardiac surgery: a randomized, double-blind clinical trial. J Cardiothorac Vasc Anesth 2011; 25: 419-24.
108. Ebade AA, Khalil MA, Mohamed AK. Levosimendan is superior to dobutamine as an inodilator in the treatment of pulmonary hypertension for children undergoing cardiac surgery. J Anesth 2013; 27: 334-9.
109. Turanlahti M, Boldt T, Palkama T, Antila S, Lehtonen L, Pesonen E. Pharmacokinetics of levosimendan in pediatric patients evaluated for cardiac surgery. Pediatr Crit Care Med 2004; 5: 457-62.

110. Lechner E, Moosbauer W, Pinter M, Mair R, Tulzer G. Use of levosimendan, a new inodilator, for postoperative myocardial stunning in a premature neonate. Pediatr Crit Care Med 2007; 8: 61-3.
111. Ryerson LM, Alexander PM, Butt WW, Shann FA, Penny DJ, Shekerdemian LS. Rotating inotrope therapy in a pediatric population with decompensated heart failure. Pediatr Crit Care Med 2011; 12: 57-60.
112. Varpula T, Rapola J, Sallisalmi M, Kurola J. Treatment of serious calcium channel blocker overdose with levosimendan, a calcium sensitizer. Anesth Analg 2009; 108: 790-2.
113. Padayachee L. Levosimendan: the inotrope of choice in cardiogenic shock secondary to takotsubo cardiomyopathy? Heart Lung Circ 2007; 16(Suppl. 3): 65-70.
114. Antonini M, Stazi GV, Cirasa MT, Garotto G, Frustaci A. Efficacy of levosimendan in Takotsubo-related cardiogenic shock. Acta Anaesthesiol Scand 2010; 54: 119-20.
115. Puttonen J, Laine T, Ramela M, Hakkinen S, Zhang W, Pradhan R, et al. Pharmacokinetics and excretion balance of OR-1896, a pharmacologically active metabolite of levosimendan, in healthy men. Eur J Pharm Sci 2007; 32: 271-7.
116. Antila S, Sundberg S, Lehtonen LA. Clinical pharmacology of levosimendan. Clin Pharmacokinet 2007; 46: 535-52.

Cite this article as: Nieminen MS, Fruhwald S, Heunks LMA, Suominen PK, Gordon AC, Kivikko M, Pollesello P. Levosimendan: current data, clinical use and future development. Heart, Lung and Vessels. 2013; 5(4): 227-245.

Source of Support: Nil. **Disclosures:** P. Pollesello and M. Kivikko are full time employees of Orion Pharma and belong to the scientific group which discovered and developed levosimendan. In the last five years, M.S. Nieminen, S. Fruhwald, A.C. Gordon and L.M.A. Heunk received limited grants and honoraria from Orion Pharma for scientific or educational activities.